Review

The Genetic Deafness in Chinese Population

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Abstract Deafness is an etiologically heterogeneous trait with many known genetic, environmental causes or a combination thereof. The identification of more than 120 independent genes for deafness has provided profound new insights into the pathophysiology of hearing. However, recent findings indicate that a large proportion of both syndromic and nonsyndromic forms of deafness in Chinese population are caused by a small number of mutations. This review is focused on syndromic and nonsyndromic deafness as well as on the latest information linking inherited mitochondrial pathologies to a variety of etiologies of sensorineural deafness in Chinese population. Better understanding of the genetic causes of deafness in Chinese population is important for accurate genetics counseling and early diagnosis for timely intervention and treatment options.

Introduction

Hearing loss (HL) is a common congenital disorder and one of the most distressing disorders affecting humanity. Deafness can result from a mutation in a single gene or from a combination of mutations in different genes; environmental causes, such as medical problems, environment exposure, trauma, and medications, or interactions between genetic and environmental factors. Worldwide, congenital deafness occurs in 1 in 1000 live births, and more than half of these cases are hereditary(Morton, 1991). Of the estimated minimum of 50% of cases with inherited hearing loss, 70% are non-syndromic and 80% of these are autosomal recessive. Non-syndromic hearing loss (NSHL) is most often sensorineural. It can be divided into DFNA (autosomal dominant deafness, 15 to 20%), DFNB (autosomal recessive deafness, 80%), DFN (X-linked deafness, 1%), and mitochondrial deafness at least 1%. To date, 114 deafness loci have been reported, 54 DFNA loci and 60 DFNB loci. More than 40 genes for monogenetic NSHL and even more for syndromic HL have been cloned (http://webhost.ua.ac.be/hhh/). According to the China Disabled Persons' Federation website, China has approximately 21 million people with hearing loss out of 60 million disabled. Although there has been a significant advance in the knowledge of the molecular basis of hereditary deafness in recent years, there have been few studies in China to evaluate the effects of genetic etiologic factors. The magnitude of the problem in China remains largely undefined. We review here the prevalence of *GJB2* mutations and other deafness genes in Chinese population, extrapolating the worldwide incidence to our 1 billion populations. Prevalence of deafness in our country is likely to be of significant public health concern.

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Nonsyndromic deafness

GJB2

Connexin 26 has been found to be the most common cause of deafness the world around. *GJB2* encodes a gap junction protein expressed in the cochlea and is thought to be important for recycling potassium ions that flow into sensory hair cells as part of the transduction current. Mutations of *GJB2*, which is responsible for DFNB1 and DFNA3, are the most frequent cause of inherited hearing loss(Cohn et al, 1999; Fuse et al, 1999; Kelley et al, 1998). More than 100 different mutations in *GJB2* have been identified in patients with non-syndromic deafness and a significant difference in the frequency and distribution of the mutations has been observed in different populations (http://www.iro.es/cx26deaf.html). They are responsible for approximately half the cases in the United States, Europe, Australia, and Israel, and have been reported in other populations as well. Most interestingly, a single mutation, 35delG, accounts for up to 70% of Northern and Southern European, as well as American Caucasian populations, with a carrier frequency ranging from 1.3% to

2.8%(Gasparini et al, 2000; Green et al, 1999). Another *GJB2* mutation, the 167delT, accounts for 40% of the pathologic alleles in the Jewish deaf population (Sobe et al, 2000) and has a 4% carrier frequency among Ashkenazi Jews(Morell et al, 1998). The 235 delC mutation is the most prevalent in Eastern Asian (Japanese, Chinese and Korean) populations, R143W in Ghana and W24X in Indian and Romany (gypsies) populations (www.gendeaf.org).

We have conducted mutation screening of *GJB2* in 118 deaf Chinese probands, including 60 from simplex and 58 from multiplex families with non-syndromic deafness, and 150 normal hearing Chinese controls. Four mutations, including 235delC, 299-300delAT, V37I, and 35delG, were found in the patients. Twenty-seven probands (22.9%) were found to carry only single *GJB2* mutations. Mutations in the exon 1 of *GJB2* were not found nor was the 342-kb deletion of *GJB6*. The deletion of cytosine at position 235 (235delC) mutation was the most prevalent mutation (20.3% of alleles), accounting for 81% of the pathologic alleles in multiplex cases and 67% in simplex cases (Liu et al, 2002). The finding that 235 delC was the most common pathologic mutation in inherited deafness attributed to *GJB2* in the Chinese population was further confirmed by Liu et al (2002). The mutant allele was found in 40 of 43 affected subjects with *GJB2*-detectable mutations. These results indicate that mutations in *GJB2* are a major cause of inherited and sporadic congenital deafness in the Chinese population. The 235delC mutation, rather than 35delG, is the most common mutation found in the Chinese deaf population.

The high frequency of the 35delG *GJB2* allelic variant in the white population has been shown to be the result of a founder effect, rather than a mutational hot spot (Van Laer et al, 2001). The 167delT mutation present in Ashkenazi Jews has also been attributed to a founder effect (Morell et al, 1998). Both the 35delG and 167delT mutations are absent or exceptionally low in Asian populations, in whom, the 235delC, is the most prevalent. This mutation accounts for up to 80% of pathogenic *GJB2* alleles among Japanese (Fuse et al, 1999; Abe et al, 2000; Kudo et al, 2000), Koreans (Park et al, 2000), and Chinese (Liu et al, 2002), with carrier rates ranging from 1.0% to 1.3%. Interestingly, the 235delC has not been detected in south Asian populations from India, Pakistan, Bangladesh, and Sri Lanka, in whom the prevalent *GJB2* mutations are W24X and W77X (Kelsell et al, 1997; Scott et al, 1998). The 235delC mutation prevalence in Japanese population has been attributed to a founder effect (Ohtsuka et al, 2003). We have showed that the high frequency of the 235delC mutation in East Asian populations is the result of a founder effect, rather than a mutation hot spot, and that 235delC among all East Asian populations is derived from a common ancestral founder (Yan et al, 2003).

GJB6

A role for *GJB6*, the gene adjacent to *GJB2* on chromosome 13, was first suggested in 1999. The most common mutation in *GJB6*, is a 342-kb deletion, which causes NSHL when homozygous, or when present on the opposite allele of a *GJB2* mutation. The *GJB6* mutation occurs in up to 20% of the hearing-impaired U.S. population (del Castillo et al, 2003). The *GJB6* deletion may account for 10% of all DFNB1 alleles with an extremely wide range based on ethnic origin. *GJB2* and *GJB6* genes are expressed in the cochlea where they can combine to form multi-unit hemichannels in the cell membrane, and function as an integral component of the potassium regulation in the inner ear.

The 342-kb deletion (*GJB6*-D13S1830) mutation is most frequent in Spain, France, the United Kingdom, Israel, and Brazil (5.9-9.7% of all DFNB1 alleles). It is less frequent in the USA, Belgium, and Australia (1.3-4.5% of all DFNB1 alleles), and very rare in Southern Italy (del Castillo et al, 2003), but has been found present in Northern Italy at frequencies similar to those of other European countries (Gualandi 2004). The deletion has also been found in another study in Germany (Bolz 2004), but not in Austria (Gunther et al, 2003), Turkey (Tekin et al, 2003; Uyguner et al, 2003), nor in China (Liu et al, 2002).

GJB3

The Connexin 31 gene (*GJB3*) mapped to chromosome 1p33-p35, encodes for a protein that is 270 amino acids long. Cx31 has been reported to be responsible for both DFNA and DFNB. The *GJB3* gene was identified by Xia et al(1998) by mutation analysis in two Chinese families with autosomal dominant nonsyndromic sensorineural deafness. A missense mutation (E183K) and a nonsense mutation (R180X) of *GJB3* were found to be associated with high-frequency hearing loss.

Following the demonstration that mutations in the *GJB3* gene can cause DFNA, we screened 25 Chinese families with DFNB to determine whether mutations at this locus can also cause DFNB. Among the 25 families, 2 contained individuals who were compound heterozygotes for GJB3 mutations. Sequence analysis in both families demonstrated an in-frame 3-bp deletion (423-425delATT); in one allele, which led to the loss

of an isoleucine residue at codon 141; and a 423A-G transiton in the other allele, which created an isoleucine 141- to -val missense mutation. Both the deletion of isoleucine-141 and its substitution by valine could alter the structure of the third conserved alpha-helical transmembrane domain (M3) and impair the function of the gap junction. The data demonstrated that Cx31, like Cx26, could be responsible for both recessive and dominant forms of non-syndromic deafness (Liu et al, 2000).

DFNB2 (*MYO7A)*

Mutations in several unconventional myosins, have been found to cause hearing loss in both humans and mice. The Myosin VIIa (*MYO7A)* protein is an unconventional myosin motor composed of a structurally conserved head, neck, and tail region that binds actin and hydrolyzes adenosine triphosphate to produce force and movement. Unconventional myosins participate in various functions that include endocytosis, regulation of ion channels, localization of calmodulin, movement of vesicles and particles in the cytoplasm and anchoring inner ear cell stereocilia.

Mutations in *MYO7A*, located at 11q13.5, are associated with Usher syndrome type 1B. They are also responsible for both autosomal dominant and recessive nonsyndromic deafness. We previously identified an in-frame 9-bp deletion in exon 22 of the MYO7A gene in affected members of the DFNA11 family (Liu et al, 1997a). We also reported mutations in the MYO7A gene in 2 of 8 families with autosomal recessive nonsyndromic deafness from the Sichuan province of China. In 1 family, 3 affected sibs were homozygous for an arg244-to-pro mutation. Furthermore, in a Chinese family with nonsyndromic autosomal recessive deafness, we found that 2 sibs were compound heterozygotes for an acceptor splice site mutation of intron 3 (IVS3AS, A-G, -2) in one allele, while the other allele carried a T insertion in exon 28, val1199insT(FS), leading to a frame shift and stop codon 28 amino acids downstream (Liu et al, 1997b).

Syndromic deafness

Usher syndrome type IC (USH1C)

Usher syndrome is an inherited disorder that is characterized by moderate to profound hearing impairment, which is present at birth or shortly thereafter, and progressive vision loss due to retinitis pigmentosa (RP), a degeneration of the retina. It is the major cause of deaf blindness. About 10,000 to 15,000 people in the United States have Usher syndrome. It is estimated to account for approximately 50% of all individuals who are both deaf and blind (Boughman et al, 1983), 18% of those with RP and 3-6% of the congenitally deaf population (Vernon, 1969). The frequency of Usher syndrome was estimated to be 3.0/100,000 in Scandinavia (Hallgren, 1959) and 4.4/100,000 in the United States (Boughman et al, 1983). Usher syndrome is both clinically and genetically heterogeneous. Three clinical subtypes have been defined based on the onset of deafness and RP, and the presence or absence of vestibular dysfunction (Keats and Corey, 1999).

Usher syndrome type I is an autosomal recessive disorder characterized by profound congenital deafness, vestibular areflexia, and progressive RP. It is the most common cause of combined deafness and blindness in developed countries. At least 11 loci have been mapped for Usher syndrome, eight of which have been cloned (Ahmed et al, 2003). Mutations in five different genes can cause USH1: *MYO7A*(USH1B) encodes the actin-based motor protein myosin VIIa (Weil et al, 1995). USH1C encodes a PDZ (postsynaptic density, disc large, zonula occludens) domain-containing protein named harmonin (Verpy et al, 2000; Bitner-Glindzicz et al, 2000). Defects in the genes encoding two cadherin-related proteins, cadherin 23 and protocadherin 15, have been shown to cause USH1D (Bolz et al, 2001; Bork et al, 2001) and USH1F (Ahmed et al, 2001; Alagramam et al, 2001), respectively. The fifth USH1 gene, USH1G, codes for a scaffold protein that contains three ankyrin-like domains and a SAM (sterile alpha motif) domain motif, and its C-terminal tripeptide presents a class I PDZ-binding motif (Weil et al, 2003).

The USH1C gene contains 28 coding exons spanning 51 kb, and three subclasses of harmonin isoforms are found as a result of alternative splicing of eight exons. The USH1C locus was mapped to chromosome 11p in Louisiana Acadian families (Keats et al, 1994; Verpy et al, 2000; Bitner-Glindzicz et al, 2000). The major isoform of harmonin contains 552 amino acids and 3 PDZ domains. Verpy et al (2000) proposed that mutation in the USH1C gene also underlies the form of nonsyndromic autosomal recessive neurosensory deafness designated DFNB18, which maps to the same region of 11p. We have indeed found in 1 of 32 Chinese multiplex families with nonsyndromic recessive deafness without RP, a C to G transversion in the alternatively spliced exon D, predicting an arginine to proline substitution at codon 608 (R608P) in the proline-, serine- and threonine-rich region of harmonin. These findings show that USH1C mutations can also cause non-syndromic deafness (Ouyang et al, 2000).

Usher syndrome type II (USH2)

Type II (USH2) is the most frequent and accounting for about 70% of all Usher syndrome. The patients tend to have less severe hearing impairment and have normal vestibular response. Currently, three loci have been identified for USH2. Of these, two genes have been cloned (Eudy et al, 1998; Weston et al, 2004). The USH2A gene is on chromosome 1q and encodes a 171 kDa protein, usherin with 1,551 amino acids (Eudy et al, 1998). The USH2A transcript is expressed primarily in the cochlea and the cells of the outer nuclear layer of the retina. At least 30 different mutations are found in USH2A, which consists of 21 exons (the first of which is noncoding), spanning at least 105 kb. The most frequent mutation, 2299delG, was found to be present in more than 20% of USH2A patients in Europe and the United States, as well as in some USH3 patients (Liu et al, 1999). In addition, the 2299delG mutation has been observed in patients whose primary disorder is RP and who report minimal hearing loss. Another USH2A mutation, Cys759Phe, was found in about 4.5% of nonsyndromic autosomal recessive RP (Rivolta et al, 2000).

We performed a mutation analysis of the USH2A gene in 23 families with Usher syndrome, 10 of which had a diagnosis of atypical Usher syndrome, from the United Kingdom and China. We found that most of the families with USH2 carried the 2299delG mutation. Of the 12 families with the 2299delG mutation, eight, including one Chinese family, had the typical USH2 phenotype (congenital moderate to severe hearing impairment, normal vestibular function, and postpubertal onset of RP). However, one Chinese patient among the 4 affected individuals from the remaining 4 families carrying the 2299delG mutation showed atypical Usher syndrome features, with progressive hearing impairment, variable vestibular function, and RP (Liu et al, 1999).

Pendred syndrome

Pendred syndrome is an inherited disorder that accounts for as much as 10% of hereditary deafness (Fraser, 1965). The syndrome is characterized by congenital severe-to-profound sensorineural hearing loss (SNHL) and euthyroid goiter. Goiter is not present at birth and develops in early puberty (40%) or adulthood. Vestibular function is abnormal in the majority of affected persons. Recessive mutations of the SLC26A4 (PDS) gene on chromosome 7q can cause sensorineural deafness with goiter (Everett et al, 1997) or NSHL without goiter (Li, 1998). Mutations in the SLC26A4 gene are identified in about 50% of multiplex families. These mutations disrupt in vitro transmembrane anion/base exchange activity of the SLC26A4 polypeptide, pendrin. (Scott, 2000).

Currently, more than 90 different mutations in SLC26A4 have been identified in patients with NSHL and a significant difference in the frequency and distribution of the mutations has been observed in different populations(http://www.medicine.uiowa.edu/pendred and dbor/Pendred% 20Syndrome.htm). Park et al. (2003) performed a mutation screening of the seven exons of the SLC26A4 gene in East Asian deaf probands with sporadic or familial severe to profound prelingual deafness, including 86 Chinese affected subjects. They identified 3 mutations (S252P, IVS7-2 A> G, N392Y) in 5 out of 86 (5.8%) Chinese probands.

Mitochondrial DNA mutations associated with syndromic and nonsyndromic deafness :

Mitochondrial (mt) pathology plays an important role in both inherited and acquired hearing loss. SNHL is present in 42 to 70% of individuals with mt disorders and can be syndromic and non-syndromic (Jacobs, 1997; Fischel-Ghodsian, 1998, 1999). MtDNA mutations have been identified in >3% of patients with SNHL (Sinnathuray, 2003). Mutations in mtDNA have also been found to be associated with both aminoglycoside-induced and nonsyndromic deafness (Fischel-Ghodsian 1999; Van Camp and Smith, 2000).

In 1992, several families with diabetes mellitus and SNHL were described, and surprisingly were found to have inherited the heteroplasmic A3243G mutation in the gene for tRNAleu (UUR). The mutation is the common cause of the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) (Reardon et al, 1992; van den Ouweland et al, 1992). The 3243A>G mutation in mtDNA frequently leads to SNHL (Gold and Rapin, 1994; Sue et al, 1998). The frequency of the A3243G mutation among the diabetic population is about 1%. The mutation has also been found in diabetic Japanese (Iwanishi et al., 1995) and Korean (Lee et al, 1997) patients. Xiang et al. (1995) and Chuang et al(1995) showed that the mutation was associated with type II diabetes in the mainland and Taiwan Chinese respectively.

The mitochondrial $tRNA^{Ser(UCN)}$ (MTTS1) appears to be a hot spot for mtDNA mutations associated with NSHL. Four deafness-associated mutations, A7445G (Fischel-Ghodsian, 1995; Reid, 1994; Sevior, 1998),

7472insC (Jaksch, 1998; Verhoeven, 1999), T7510C (Hutchin, 2000) and T7511C (Sue, 1999; Ishikawa, 2002; Chapiro, 2002) have been identified in this gene.

The mitochondrial 12S rRNA(MTRNR1) is another hot spot for mtDNA mutations.

The homoplasmic A1555G mutation of this rRNA has been associated with aminoglycoside-induced and NSHL in many families of different population (Hutchin et al, 1993; Prezant et al, 1993; Matthijs et al, 1996; Pandya et al, 1987; Estivill et al, 1998; del Castillo et al, 2003; Li et al, 2004a, b; Young et al, 2005).

Mutations at position 961 of MTRNR1 have also been implicated in aminoglycoside ototoxicity and non-syndromic deafness (Casano et al, 1999; Li et al, 2004a). Furthermore, the T1095C mutation in the same rRNA has also been shown to be associated with hearing loss (Li 2005;Wang et al, 2005). Most recently, the homoplasmic C1494T mutation in the highly conserved decoding site of this rRNA has been associated with both aminoglycoside-induced and non-syndromic hearing loss in a large Chinese family (Li, 2005).

Li et al. (2005) conducted a systematic mutational screening of the mitochondrial 12S rRNA gene in a Chinese pediatric population with sporadic aminoglycoside-induced and NSHL. They showed that aminoglycoside ototoxicity is responsible for 48% of cases. Mu-

Table1. Mutations underlying syndromic and nonsyndromic hearing loss in Chinese families

Hearing impairment	Gene and protein	Chr.Location(Locus)	Mutation	Refs
Nonsyndromic	*GJB2 Connexin 26*	13q11-12 (DFNB1)	235delC	Liu, 2002
			299-300delAT	Liu, 2002
			V37I	Liu, 2002
			35delG	Liu, 2002
	MYO7A myosin VIIA	11q13.5(USH1B)	R244P	Liu, 1997a
			IVS3-2A＞G	Liu, 1997a
			3596_3597ins T	Liu, 1997a
	GJB3	13q12(DFBA2)	R180X	Xia, 1998
			E183K	Xia, 1998
			423delATT;	Liu, 2000
			I141V	Liu, 2000
	12S rRNA	MT	A827G	Li, 2005
			961C insertion	Li, 2005
			T1095C	Li, 2005
				Zhao, 2005
				Wang, 2005
			C1494T	Li, 2005
			1555A＞G	Hu, 1991
Syndromic	*USH1C harmonin*	11p15.1 (DFNB18)	P608R	Ouyang, 2002
	USH2A usherin	1q41 (USH2A)	2299delG	Liu, 1999
	SLC26A4 Pendrin	7q31(DFNB4)	IVS7-2A	Yong AM, 2001
			N392Y	Hu, 2005
			S448X	Hu, 2005
			G316X	Dai, 2005
			919-2A＞G	Dai, 2005
	$tRNA^{Leu(UUR)}$	MT	3243A>G	Xiang, 1995

tations at position 961 in the MTRNR1gene accounted for ~1.7% and 4.4% cases of aminoglycoside-induced and NSHL, respectively in this Chinese clinical population. The frequency of the A1555G mutation was ~ 13% and ~2.9% in these Chinese pediatric subjects with aminoglycoside-induced and non-syndromic hearing loss, respectively.

Deafness genes in Chinese families

Deafness genes segregating non-syndromic/syndromic autosomal recessive inheritance, contribute to a high percentage of genetic cause of deafness in China. Localization and cloning of deafness genes have been performed in China since 1990s. Gene mapping and mutations screening have been carried out in large multi-generational families. The genes associated with deafness in Chinese families have been reported in the following studies: (1) *GJB3* was cloned in China and mapped to human chromosome 1p33-p35. Mutation analysis revealed that mutations of the gene were associated with high-frequency hearing loss(Xia et al., 1998). (2) Xiao et al (2001) mapped the DFNA39 locus and showed that distinct mutations in the dentin sialophosphoprotein gene(DSPP) are responsible for the clinical manifestations of Dentinogenesis imperfecta with or without DFNA39. (3) Xia et al (2002) described a Chinese pedigree with autosomal dominant nonsyndromic hearing loss mapped to chromosome 5q31.1-q32. (4) Yu et al (2003) reported a second mutation in the DFNA5 gene, leading to skipping of exon 8 of DFNA5. (5) Wang et al (2004a) performed a genetic analysis in a Chinese deaf-mute family with X-linked recessive inheritance. (6) Wang et al (2004b) reported a Y-linked inheritance of non-syndromic hearing impairment in a large Chinese family. (7) The DFNA41 locus was mapped on the long arm of chromosome 12q24-qter(Blanton et al, 2002; Yan et al, 2005a). (8) Yan et al(2005b) reported mapping of the DFNA53 locus on the long arm of chromosome 14 at 14q11.2-q12, through studying a large multi-generational Chinese family with post-lingual, high frequency hearing loss that progressed to involve all frequencies. (9) *SLC26A4* defects(DFNB4) on 7q31 were reported to be the causes of Pendred syndrome(Dai P et al 2005).

Concluding remarks

The *GJB2* gene accounts for approximately 13-26.7% of the molecular causes of deafness in China (Liu, 2002), indicating that there are several more genes involved in the causation of deafness that need to be unfolded. The 235delC mutation in *GJB2* has been shown to be the most prevalent mutation (20.3% of alleles), accounting for 81% of the pathologic alleles in multiplex cases and 67% in simplex cases (Liu, 2002). Mutations at 961 position, T1095C and 1555A> G mutations in 12S rRNA are hot spot mutations in Chinese population. Mutations that are involved in syndromic and nonsyndromic deafness found in Chinese population are reported in Table 1. Therefore, testing for these mutations is the first step toward a molecular diagnosis of deafness. Thorough investigation of the etiology of hearing loss is necessary for accurate genetic counseling and for the implementation and assessment of any future gene therapy.

Acknowledgements

This study is supported by grants from NIH DC R01 05575 (USA) and NSFC 30528025 (China) to LIU Xuezhong.

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